

Inventor : DONG, Zheng Xin et al.
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COMPLETE LISTING OF ALL CLAIMS, WITH MARKINGS AND STATUS IDENTIFIERS
(Currently amended claims showing deletions ~~by strikethrough~~ and additions by underlining)

What is claimed is:

1 (original): A compound of formula (I),
$$(R^2R^3) - A^7 - A^8 - A^9 - A^{10} - A^{11} - A^{12} - A^{13} - A^{14} - A^{15} - A^{16} - A^{17} - A^{18} - A^{19} - A^{20} - A^{21} - A^{22} - A^{23} - A^{24} - A^{25} - A^{26} - A^{27} - A^{28} - A^{29} - A^{30} - A^{31} - A^{32} - A^{33} - A^{34} - A^{35} - A^{36} - A^{37} - R^1 ,$$

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, D-His, Tyr, 3-Pal, 4-Pal, Hppa, Tma-His, Amp or deleted, provided that when A^7 is Ura, Paa, Pta or Hppa then R^2 and R^3 are deleted;

A^8 is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala, Arg or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, Ala, D-Ala, Phe or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β -Nal, Cha, Trp or X^1 -Phe;

A^{13} is Thr or Ser;

A^{14} is Ser, Thr, Ala or Aib;

A^{15} is Asp, Ala, D-Asp or Glu;

A^{16} is Val, D-Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala, D-Ala, Tba or Cha;

A^{17} is Ser, Ala, D-Ala, Aib, Acc or Thr;

A^{18} is Ser, Ala, D-Ala, Aib, Acc or Thr;

A^{19} is Tyr, D-Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β -Nal, Amp or X^1 -Phe;

A^{20} is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X^1 -Phe;

A^{21} is Glu, Ala or Asp;

A^{22} is Gly, Acc, Ala, D-Ala, β -Ala or Aib;

A^{23} is Gln, Asp, Ala, D-Ala, Aib, Acc, Asn or Glu;

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A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;

A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁶ is Lys, Ala, 3-Pal, 4-Pal, Arg, hArg, Orn, Amp, HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁷ is Glu, Ala, D-Ala or Asp;

A²⁸ is Phe, Ala, Pal, β-Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;

A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala, Tba or Phe;

A³⁰ is Ala, Aib, Acc or deleted;

A³¹ is Trp, Ala, β-Nal, 3-Pal, 4-Pal, Phe, Acc, Aib, Cha, Amp or deleted;

A³² is Leu, Ala, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe, Ala or deleted;

A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, X¹-Phe, Tba, Gaba or deleted;

A³⁴ is Lys, Arg, hArg, Orn, Amp, Gaba,

HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

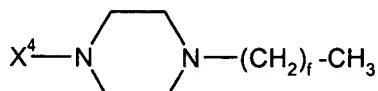
A³⁵ is Gly or deleted;

A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, Amp, HN-CH((CH₂)_n-NR¹⁰R¹¹)-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

A³⁷ is Gly or deleted;

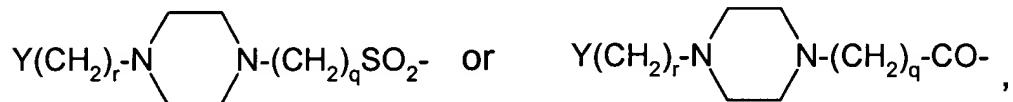
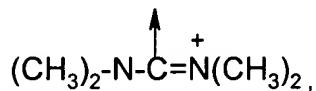
X¹ for each occurrence is independently selected from the group consisting of (C₁-C₆)alkyl, OH and halo;

R¹ is OH, NH₂, (C₁-C₁₂)alkoxy, or NH-X²-CH₂-Z, wherein X² is a (C₁-C₁₂)hydrocarbon moiety, and Z is H, OH, CO₂H or CONH₂;



X³ is or -C(O)-NHR¹², wherein X⁴ for each occurrence is independently -C(O)-, -NH-C(O)- or -CH₂-, and f for each occurrence is independently an integer from 1 to 29;

each of R² and R³ is independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is C(O)X⁵ in which X⁵ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, hydroxynaphthyl(C₁-C₃₀)alkyl,



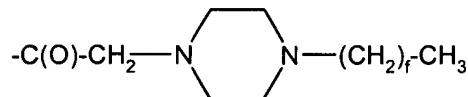
(a)

(b)

where Y is H or OH, r is 0 to 4 and q is 0 to 4; e for each occurrence is independently an integer from 1 to 4;

n for each occurrence is independently an integer from 1-5; and

R¹⁰ and R¹¹ for each occurrence is each independently H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



, provided that when R¹⁰ is

(C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



, R¹¹ is H or (C₁-C₃₀)alkyl; and

R¹² is (C₁-C₃₀)alkyl;

with the proviso that:

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36), or

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-37)NH₂ (SEQ ID NOS: 1, 2) or hGLP-1(7-36, or -37)OH (SEQ ID NOS: 3, 4);

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, or -37)NH₂ (SEQ ID NOS: 1,2) or hGLP-1(7-36, or -37)OH (SEQ ID NOS: 3, 4) wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not

[Lys²⁶(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E (SEQ ID NOS: 5-8), [Lys³⁴(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E (SEQ ID NOS: 9-12), [Lys^{26,34}-bis(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E (SEQ ID NOS: 13-16), [Arg²⁶, Lys³⁴(N^ε-alkanoyl)]hGLP-1(8-36, or -37)-E (SEQ ID NOS: 17-20), or [Arg^{26,34}, Lys³⁶(N^ε-alkanoyl)]hGLP-1(7-36, or -37)-E, wherein E is -OH or -NH₂ (SEQ ID NOS: 21-24);

(iv) a compound of formula (I) is not

Z-hGLP-1(7-36, or -37)-OH, Z-hGLP-1(7-36, or -37)-NH₂, where Z is selected from the group consisting of

(a) [Arg²⁶] (SEQ ID NOS: 25-28), [Arg³⁴] (SEQ ID NOS: 29-32), [Arg^{26,34}] (SEQ ID NOS: 33-36), [Lys³⁶], [Arg²⁶, Lys³⁶] (SEQ ID NOS: 41-44), [Arg³⁴, Lys³⁶] (SEQ ID NOS: 45-46), [D-Lys³⁶], [Arg³⁶] (SEQ ID NOS: 37-40), [D-Arg³⁶] (SEQ ID NOS: 3, 4, 1, 2), [Arg^{26,34}, Lys³⁶] (SEQ ID NOS: 49-52) or [Arg^{26,36}, Lys³⁴] (SEQ ID NOS: 25-28);

(b) [Asp²¹] (SEQ ID NOS: 53-56);

(c) at least one of [Aib⁸] (SEQ ID NOS: 57-60), [D-Ala⁸] and [Asp⁹] (SEQ ID NOS: 61-64); and

(d) [Tyr⁷] (SEQ ID NOS: 65-68), [N-acyl-His⁷] (SEQ ID NOS: 69-72), [N-alkyl-His⁷] (SEQ ID NOS: 73-76), [N-acyl-D-His⁷] or [N-alkyl-D-His⁷];

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and

(vi) a compound of formula (I) is not [N-Me-Ala⁸]hGLP-1(8-36 or -37) (SEQ ID NOS: 77, 78), [Glu¹⁵]hGLP-1(7-36 or -37) (SEQ ID NOS: 79, 80), [Asp²¹]hGLP-1(7-36 or -37) (SEQ ID NOS: 53, 54) or [Phe³¹]hGLP-1(7-36 or -37) (SEQ ID NOS: 81, 82).

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2 (original): A compound according to claim 1 or a pharmaceutically acceptable salt thereof wherein A¹¹ is Thr; A¹³ is Thr; A¹⁴ is Ser, Aib or Ala; A¹⁷ is Ser, Ala, Aib or

D-Ala; A¹⁸ is Ser, Ala, Aib or D-Ala; A²¹ is Glu or Ala; A²³ is Gln, Glu, or Ala; and A²⁷ is Glu or Ala.

3 (original): A compound according to claim 2 or a pharmaceutically acceptable salt thereof wherein A⁹ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, D-Val, Acc, Aib, Ala, Tle or D-Ala; A¹⁹ is Tyr, 3-Pal, 4-Pal or D-Tyr; A²⁰ is Leu, Acc, Cha, Ala or Tle; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Orn,

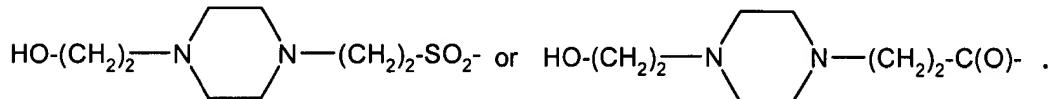
HN-CH((CH₂)_n-NH-R¹⁰)-C(O); A²⁸ is Phe or Ala; A²⁹ is Ile, Acc or Tle; A³⁰ is Ala, Aib or deleted; A³¹ is Trp, Ala,

3-Pal, 4-Pal or deleted; A³² is Leu, Acc, Cha, Ala or deleted; A³³ is Val, Acc, Ala, Gaba, Tle or deleted.

4 (original): A compound according to claim 3 or a pharmaceutically acceptable salt thereof wherein A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly, Ala, D-Ala or Phe; A¹² is Phe, A6c or A5c; A¹⁶ is Val, Ala, Tle, A6c, A5c or D-Val; A²⁰ is Leu, A6c, A5c, Cha, Ala or Tle; A²² is Gly, Aib, β -Ala, L-Ala or D-Ala; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c, A5c or Tle; A³² is Leu, A6c, A5c, Cha, Ala or deleted; A³³ is Val, A6c, A5c, Ala, Gaba, Tle or deleted.

5 (original): A compound according to claim 4 or a pharmaceutically acceptable salt thereof wherein R¹ is OH or NH₂.

6 (original): A compound according to claim 5 or a pharmaceutically acceptable salt thereof wherein R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl,



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7 (original): A compound according to claim 1
wherein said compound is

[D-Ala⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂;
[Ala^{18,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 83);
[Ala^{16,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 84);
[Ala^{14,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 85);
[Ala^{22,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 86);
[Hppa⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 87);
[Ala^{15,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 88);
[Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-35)-NH₂ (SEQ ID NO: 89);
[Ala^{22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 90);
[Ala^{15,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 91);
[Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 92);
[Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 93);
[Ala^{21,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 94);
[Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 95);
[Ala^{22,23,27,32}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 96);
[Ala^{22,23,26,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 97);
[Ala^{22,23,27,31}, 3-Pal¹⁹, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 98);
[Ala^{22,23,27,28}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 99);
[Ala^{22,23,27,29}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 100);
[Ala^{23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 101);
[Ala^{20,22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO:
102);
[Ala^{22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO: 103);
[Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂ (SEQ ID NO:
104);
[D-Ala¹⁰, Ala^{22,23,27}, 3-Pal^{19,31}, Gaba³³]hGLP-1(7-33)-NH₂;
[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH₂;
[Ala^{17,23,27}, 3-Pal^{19,26,31}]hGLP-1(7-34)-NH₂ (SEQ ID NO: 105);
[D-Ala⁸, Ala¹⁷, 3-Pal^{19,31}]hGLP-1(7-34)-NH₂;
[Ala^{17,23,27}, 3-Pal^{19,31}]hGLP-1(7-34)-NH₂ (SEQ ID NO: 106);
[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Tle²⁹]hGLP-1(7-34)-NH₂;

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[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Tle¹⁶]hGLP-1(7-34)-NH₂;
[D-Ala⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala²², Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[Aib⁸, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 107);
[D-Ala⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂;
[Aib⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂ (SEQ ID NO: 108);
[Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 109);
[Ala^{17,23,27}, 3-Pal^{19,31}, Tle³³, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 110);
[Tle¹⁶, Ala^{17,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 111);
[N-Me-D-Ala⁸, Ala^{17,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂;
[Aib⁸, Ala^{17,18,22,23,27}, 3-Pal^{19,31}]hGLP-1(7-33)-NH₂ (SEQ ID NO: 112);
[Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle^{16,20}, Gaba³⁴]hGLP-1(7-34)-NH₂ (SEQ ID NO: 113);
[D-Ala⁸, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Tle¹⁶, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,22}, Ala^{17,18,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,18}, Ala^{17,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂;
[D-Ala^{8,17}, Ala^{18,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂; or
[D-Ala⁸, Ala^{17,18,22,23,27}, 3-Pal^{19,31}, Gaba³⁴]hGLP-1(7-34)-NH₂; or a pharmaceutically acceptable salt thereof.

8 (original): A compound according to claim 1 wherein said compound is

[Aib⁸, A6c³²]hGLP-1(7-36)NH₂ (SEQ ID NO: 114);
[A6c^{20,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 115);
[Aib⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 116);
[(Tma-His)⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 117);
[A6c⁸]hGLP-1(8-36)-NH₂ (SEQ ID NO: 118);
[A6c⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 119);
[A6c^{16,20}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 120);
[A6c^{29,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 121);
[A6c²⁰, Aib²⁴]hGLP-1(7-36)-NH₂ (SEQ ID NO: 122);

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[Aib²⁴, A6c^{29,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 123);
[A6c^{16,29,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 124);
[Ura⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 125);
[Paa⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 126);
[Pta⁷]hGLP-1(7-36)-NH₂ (SEQ ID NO: 127);
[N-Me-Ala⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 128);
[N-Me-D-Ala⁸]hGLP-1(7-36)-NH₂;
[N-Me-D-Ala⁸]hGLP-1(8-36)-NH₂;
[N-Me-Gly⁸]hGLP-1(7-36)-NH₂ (SEQ ID NO: 129);
[A5c⁸]hGLP-1(7-36) (SEQ ID NO: 130);
[N-Me-Glu⁹]hGLP-1(7-36)-NH₂ (SEQ ID NO: 131);
[A5c⁸, A6c^{20,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 132);
[Aib⁸, A6c³²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 133);
[Aib^{8,25}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 134);
[Aib^{8,24}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 135);
[Aib^{8,30}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 136);
[Aib⁸, Cha²⁰]hGLP-1(7-36)-NH₂ (SEQ ID NO: 137);
[Aib⁸, Cha³²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 138);
[Aib⁸, Glu²³]hGLP-1(7-36)-NH₂ (SEQ ID NO: 139);
[Aib⁸, A6c²⁰]hGLP-1(7-36)-NH₂ (SEQ ID NO: 140);
[Aib⁸, A6c^{20,32}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 141);
[Aib^{8,22}]hGLP-1(7-36)-NH₂ (SEQ ID NO: 142);
[Aib⁸, β -Ala²²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 143);
[Aib⁸, Lys²⁵]hGLP-1(7-36)-NH₂ (SEQ ID NO: 144);
[Aib⁸, A6c¹²]hGLP-1(7-36)-NH₂ (SEQ ID NO: 145);
[Aib⁸, A6c²⁹]hGLP-1(7-36)-NH₂ (SEQ ID NO: 146);
[Aib⁸, A6c³³]hGLP-1(7-36)-NH₂ (SEQ ID NO: 147);
[Aib^{8,14}]hGLP-1(7-36)NH₂ (SEQ ID NO: 148);
[Aib^{8,18}]hGLP-1(7-36)NH₂ (SEQ ID NO: 149); or
[Aib^{8,17}]hGLP-1(7-36)NH₂ (SEQ ID NO: 150); or a
pharmaceutically acceptable salt thereof.

9 (original): A pharmaceutical composition
comprising an effective amount of a compound according to

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claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

10 (withdrawn): A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

11 (withdrawn): A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, and hypertension, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

12 (withdrawn): A method according to claim 11 wherein said disease is Type I diabetes or Type II diabetes.